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Probable catastrophic antiphospholipid syndrome (CAPS)

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ABSTRACT We describe the case of a 53-year-old man who presented with a cerebellar stroke. He developed a thrombus in his left ileo-femoral vein, and his IgG anticardiolipin antibody turned out to be positive. He then developed thrombosis of the right ileo-femoral vein while well anticoagulated with warfarin. Despite aggressive anticoagulation he developed livedo reticularis, pulmonary embolism, adult respiratory distress syndrome and renal failure over a few weeks and eventually died from a large gastrointestinal bleeding. He probably had catastrophic antiphospholipid syndrome (CAPS) or Asherson's syndrome, which has a high mortality. We discuss the current treatment options available for such a patient.

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CASE HISTORY

A 53-year-old man presented with a sudden onset of dizziness, diplopia, vomiting, imbalance and impaired speech. He had a 40 pack-year history of smoking, although having given up seven years ago, and consumed 30 units of alcohol per week. He had no significant medical history other than distal proctocolitis, which was controlled with aminosalicylate. He had no relevant family history.

Clinical examination revealed central obesity, horizontal and vertical nystagmus, right-sided Horner's syndrome, vertical diplopia, mild dysarthria and right-sided dis-coordination. A computerised tomography scan showed infarction of the right cerebellum and adjacent midbrain. Magnetic resonance imaging demonstrated extensive acute right cerebellar infarction extending into the midbrain. This type of infarction is seen to involve both the right superior cerebellar (see Figure 1a) and anterior inferior cerebellar (see Figure 1b) arterial territories. Subsequent magnetic resonance angiography of the circle of Willis and neck vessels showed right superior cerebellar and possible right posterior cerebral arterial involvement. There were also right supratentorial lacunar infarcts, but no stenosis of carotid or vertebral arteries. The patient was in sinus rhythm, and his echocardiogram was normal. His initial full blood count, liver function, renal function, clotting screen, C-reactive protein and erythrocyte sedimentation rate were normal.

The patient was started on aspirin, dipyridamole and simvastatin (total cholesterol 4.9, high density lipoprotein 0.69). Compression stockings were used for his lower limbs because of his poor mobility. While being rehabilitated three weeks later, he developed deep venous thrombosis (DVT) in the left ileo-femoral veins. Treatment was switched over to warfarin. It took two weeks to bring his international normalised ratio (INR) to therapeutic range (2–3). After a further three weeks he developed another DVT in the right ileo-femoral veins, while his INR was reasonable (the lowest was 2.2 and the highest 4.1).

At that time the results of his auto-antibody screen became available: IgG anti-cardiolipin antibody 60.2 GPL u/ml (normal range 0–10); IgM anti-cardiolipin antibody 0.7 MPL u/ml (1–7); anti-nuclear antibody was weakly positive; rheumatoid factor <5 iu/ml (0–20); dsDNA antibody 10 iu/ml (0–50). His anti-mitochondrial antibody, anti-smooth muscle antibody, gastric parietal cell antibody and liver/kidney microsomal antibodies were negative. His platelet count remained on the higher side (397–465) and hereditary clotting tests (including Factor V Leiden, prothrombin gene mutation, antithrombin III, activated protein C resistance, protein C and protein S level) were normal.

The haematologist suggested increasing the INR target to 4 in view of the recurrent DVT on the background of antiphospholipid syndrome (APS). The patient developed a skin rash suggestive of livedo reticularis, and developed pulmonary embolism after a week despite a higher INR, which ranged from 3.1 to 6.2. An inferior vena cava filter was inserted via jugular vein, and aggressive anticoagulation was continued. After another week the patient developed acute respiratory distress syndrome (see Figure 2) and went into renal failure. There was no evidence of infection, connective tissue disease or malignancy. He did not have any history of trauma. His repeat IgG anti-cardiolipin antibody level was 82.1 GPL u/ml, and the IgM anti-cardiolipin antibody was 1.9 MPL u/ml after eight weeks. The patient had an episode of a small amount of

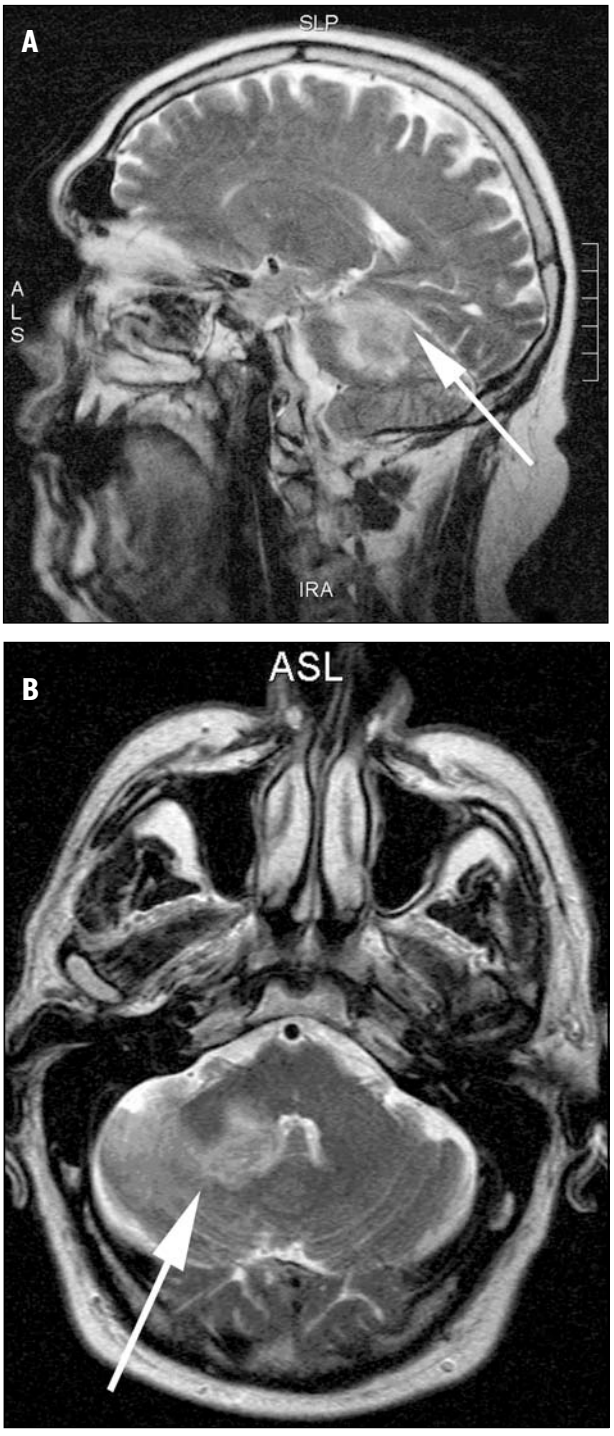

FIGURE 1 Magnetic resonance imaging scans from a 53-year-old man presenting with a cerebellar stroke, whose symptoms included a horizontal and vertical nystagmus, right-sided Horner's syndrome, vertical diplopia, mild dysarthria and right-sided discoordination. The CT scan showed infarction of the right cerebellum and adjacent midbrain. Scans A and B show extensive acute right cerebellar infarction extending into the midbrain. Scan A shows the involvement of the right superior cerebellar artery, and scan B the anterior inferior cerebellar artery. Subsequent MRA of the circle of Willis and neck vessels showed right superior cerebellar and possibly right posterior cerebral arterial involvement. There were also right supratentorial lacunar infarcts, but no stenosis of carotid or vertebral arteries.

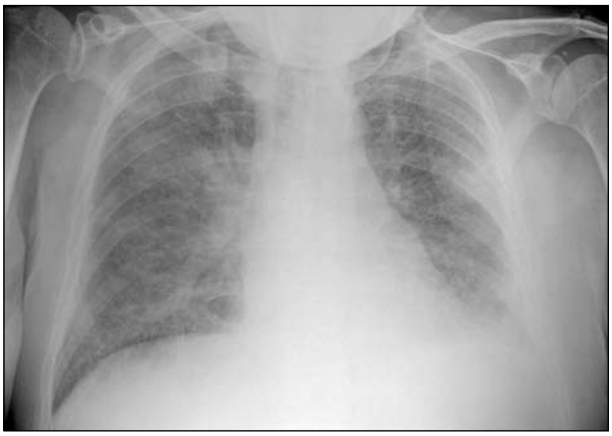

FIGURE 2 This chest X-ray shows the development in the patient of an extensive diffuse bilateral alveolar opacification just prior to death, following the development of an acute respiratory distress syndrome and renal failure. Three weeks after the stroke the patient developed a DVT in his left ileo-femoral veins, followed by a DVT in the right ileo-femoral veins three weeks later and, after a further week, a pulmonary embolism, despite aggressive anticoagulation and the insertion of an inferior vena cava filter.

haematemesis, while the INR was 4.0 despite his being on a proton pump inhibitor. While waiting to be stabilised for endoscopy, the patient died from an episode of large melaena.

DISCUSSION

Antiphospholipid syndrome is an antibody-mediated hypercoagulable state characterised by recurrent arterial and venous thromboembolism. Catastrophic APS (CAPS), also known as Asherson's syndrome, was first described in 1992.[1] This subset represents fewer than 1% of all patients with APS and has an acute and accelerated course characterised by multiple vascular occlusive events involving three or more organs over a short period of time.[2] Although we did not find any evidence of infection in our patient, in a series of 100 patients with APS associated with infection, pulmonary involvement was 39%, skin involvement 36% and renal involvement 35%.[3] In another series of 47 patients, acute respiratory distress syndrome (ARDS) was the dominant pulmonary manifestation of CAPS.[4]

There are several possible hypotheses for thrombosis in APS. Oyama et al. described how the anti-cardiolipin antibody binds to cardiolipin through beta 2-glycoprotein I, which is a phospholipid-binding plasma protein that inhibits generation of factor Xa on the surface of activated platelets. Therefore, the thromboembolic complications may result from anti-cardiolipin antibody inhibition of the formation of the active form of beta 2-glycoprotein I or its physiological function.[5]

Oyama et al. also felt that the impaired production of thrombomodulin, a thrombin receptor present on the endothelial cell membrane as a result of endothelial cell

damage, reduces protein C activation and therefore encourages intravascular coagulation. Asherson described various infections, including hepatitis C and HIV, acting as precipitating factors that contribute to the development of CAPS by causing endothelial damage resulting in gross fibrinolytic disturbance. This may be associated with malignancy, when it is known as Trousseau's syndrome.

Aspirin and moderate-intensity warfarin appear equally effective for preventing recurrent stroke in patients with a single positive antiphospholipid antibody test.[6] In a prospective study, high-intensity (INR 3.1–4.0) warfarin was found not to be superior to moderate-intensity (INR 2.0–3.1) warfarin therapy in cases of recurrent thromboembolism.[7]

Recurrent thromboembolic events can be extremely difficult to treat. Anecdotally, immunomodulatory therapies have been used in combination with an aggressive antithrombotic strategy,[8] including steroids, cyclophosphamide and rituximab. There are no data concerning how long these patients should be treated with immunosuppressive therapy. Plasma exchange and intravenous immunoglobulin can be added in life-threatening situations, although the latter increases the risks of further thromboembolism in patients with previous thromboembolic diseases, particularly when used in high doses or infused rapidly.[9] Despite aggressive treatment and intensive care unit management, CAPS has a high mortality (48–60% in different studies), primarily attributable to multi-organ failure.[10]

We did not use steroids as the patient developed the complications described above over a period of weeks rather than days, and subsequently developed haematemesis, despite being on a proton pump inhibitor. In retrospect, we felt we could have tried steroids or plasma exchange in addition to intensifying the warfarin therapy.

CONCLUSION

Catastrophic antiphospholipid syndrome causes recurrent thromboembolic events that can be extremely difficult to treat and often require an intensive care unit setting. If an APS patient develops respiratory symptoms, ARDS should be considered and managed accordingly. Immunosuppressive therapy and plasma exchange should be considered in patients not responding to anti-coagulation treatment alone.

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